Quarterly Surveillance Report

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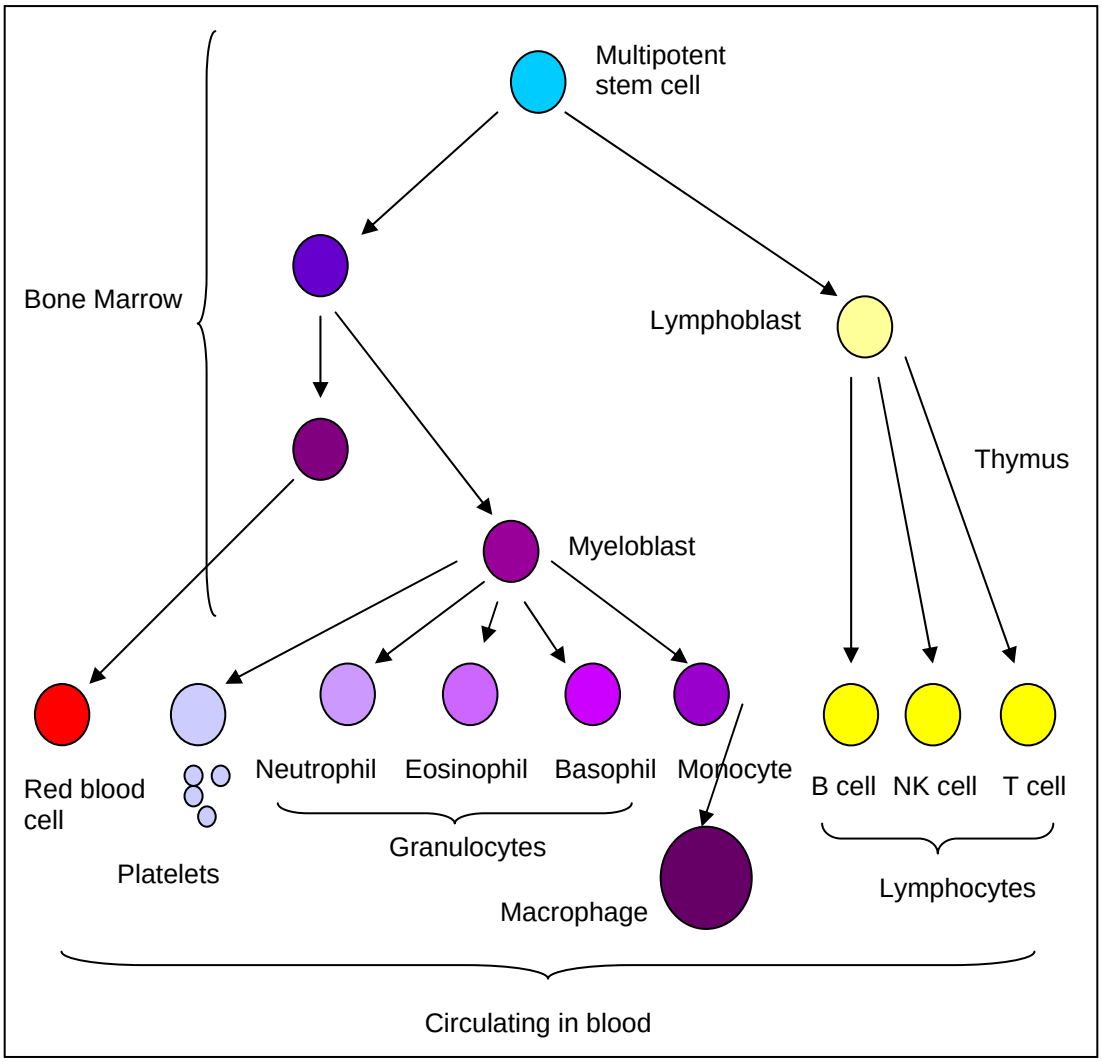
Leukemia, Lymphoma, and Myeloma

All blood cells originate from multipotent stem cells in the bone marrow. The body directs the bone marrow to regulate production of each cell type using a variety of hormones and other chemical signals, so blood cell development usually meets the needs of the body very precisely. Red blood cells carry oxygen to all tissues of the body. Platelets are

Figure 1. Simplified diagram of the origins of blood cells

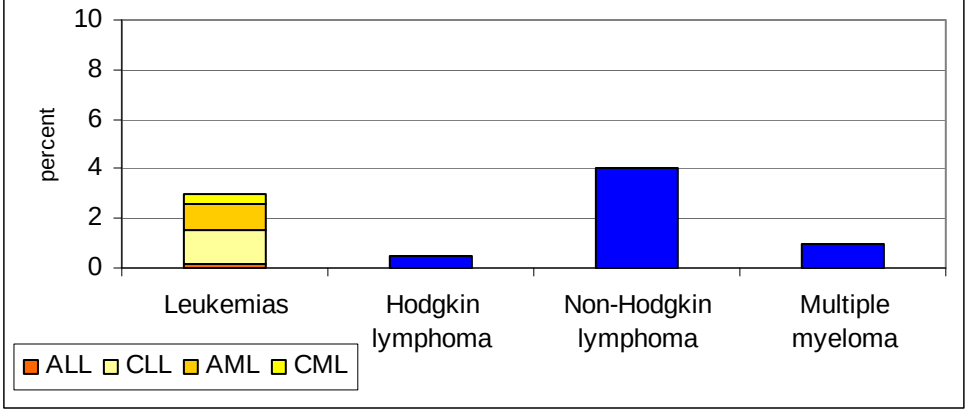


essential for blood clotting. Granulocytes or white blood cells (neutrophils, eosinophils, and basophils) and lymphocytes are the basis of the immune response.

Each arrow in Figure 1 represents a complex and highly regulated process and each is an opportunity for an error in the control of cell production. Leukemias, lymphomas, and myelomas arise when the processes are disordered. They are collectively called hematological neoplasms, or cancers of the blood and the tissues that produce blood cells. They are classified by the type of cells affected and by the aggressiveness of the disease. The causes of these disorders are not usually known for any individual, but risk factors for some have been identified on a population basis.

All hematological cancers combined account for less than 10% of cancer in Montana (Figure 2). Non-Hodgkin lymphoma ranks 6th among cancers in Montana, the leukemias combined are 8th, multiple myeloma is 17th, and Hodgkin lymphoma is 23rd. Individually, the four common subtypes of leukemia each account for less than 1% of all cancer.

Figure 2. Hematological Cancers as Percent of Total Cancer
Montana Central Tumor Registry 1980-2005



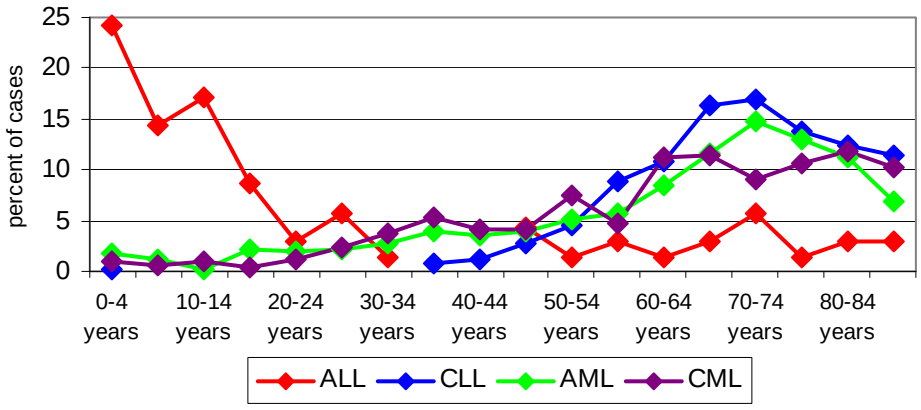
Leukemia

Blast cells (myeloblasts and lymphoblasts) are immature stages in the development of normal mature granulocytes and lymphocytes. Leukemia occurs when the bone marrow produces abnormal blast cells that do not mature properly. The blast cells cannot perform immune functions so the body's defenses against infection are compromised. Excess blast cells may be released into circulation or they may accumulate in the bone marrow where they interfere with other necessary functions of the marrow, such as the production of other white blood cells, red blood cells, and platelets. As a result, the symptoms of leukemia may be complex and include evidence of disruption of many bone marrow functions and a wide variety of signs and symptoms throughout the body.

Leukemia is classified by the cell type involved (lymphoblasts or myeloblasts) and how aggressively the disease progresses (acute or chronic). In acute leukemia, abnormal blasts are produced rapidly, interfering with normal functions of the bone marrow, and immune function is very poor. There may be no normal mature lymphocytes or myelocytes in acute leukemia. In chronic leukemia, abnormal cells are produced at a lower rate, may be slightly more mature than in acute leukemia, and some mature cells may also be produced, but immune function gradually deteriorates and overall bone marrow function gradually declines.

Acute lymphoblastic leukemia (ALL; also called acute lymphocytic leukemia or acute lymphoid leukemia) is the most common cancer of childhood, accounting for almost one third of all cancers diagnosed in children under 15 (Figure 3). More than one half of all cases of ALL occur in children under 15 and one quarter occur in children under five. The other types of leukemia (chronic lymphocytic leukemia or CLL; acute myeloid leukemia or AML, also called acute non-lymphocytic leukemia, acute myelogenous leukemia, or acute myeloblastic leukemia; and chronic myeloid leukemia or CML, also called chronic myelocytic leukemia, chronic myelogenous leukemia, or chronic granulocytic leukemia) are more common in adults than in children.

Figure 3. Age at Diagnosis of Leukemia
Montana Central Tumor Registry 1980-2005



Each type of leukemia has its own constellation of established risk factors. Studies of Japanese survivors of atomic bomb blasts in World War II have shown that exposure to catastrophic levels of radiation in childhood increase the risk of ALL, AML, and CML, but not CLL. A history of therapeutic radiation for treatment of other primary cancers and other medical conditions is also associated with a slightly increased risk of subsequently developing ALL, AML, and CML. Prior to about 1960, occupational exposures to radiation among radiologists, x-ray technicians, workers in the nuclear arms

industry, and military personnel exposed to above ground nuclear testing were associated with increased risk of AML in adults. Occupational exposures to radiation from these sources have been greatly reduced in recent years.

Because ALL is most often a cancer of early childhood, there have been many investigations of prenatal exposures and parents' lifestyle factors as possible causes of ALL but most studies have been inconclusive or inconsistent.[1] Apart from radiation and benzene exposures, there are no clearly documented risk factors for childhood ALL. Parental behaviors such as smoking, alcohol consumption, or occupational chemical exposures have not been consistently linked to childhood ALL.

Two extensive studies of possible environmental causes of childhood ALL have been conducted recently, one in Nevada and one in Arizona.[2, 3] Communities in both states experienced notable excesses of ALL and citizens were concerned about the possible risks posed by active military installations, environmental fuel contamination, high energy electromagnetic fields, and abandoned mine sites. Both studies investigated a large number of chemicals (including heavy metals, pesticides, polychlorinated biphenols, and volatile organic compounds) and found no evidence that exposure to these was associated with leukemia. However, in both communities, a particular genetic variation was found to be associated with an increased risk of ALL. The investigators suggested that children with this variation might be especially susceptible to developing ALL.

Smoking is a documented risk factor for adult AML and a suspected risk factor for adult CML. It has been estimated that one in five cases of AML can be attributed to smoking.[4] There have been few other well-designed studies of behavioral and lifestyle factors including diet or alcohol consumption as risk factors for leukemia and no increased risks have been documented.

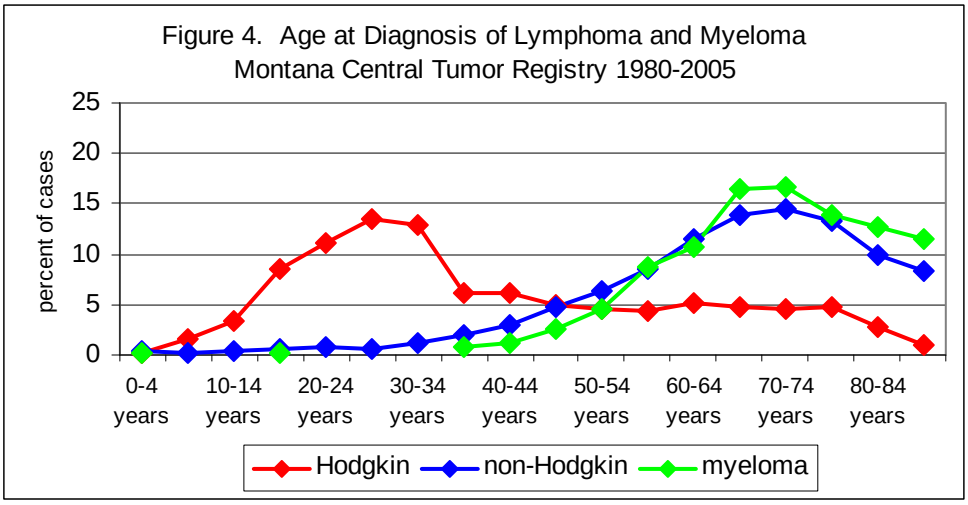
There have been many studies of chemical exposures on the risk of leukemia in adults but the results are inconsistent. This is due in part to the relative rarity of leukemia and in part to the fact that different types of leukemia were not always considered individually in the studies. In addition, job titles were usually used as proxy measures leading to imprecise estimates of exposure. The only well-documented association is increased risk of AML or CML with occupational exposure to benzene.[5] Studies of other risk factors for leukemia, including farming and ranching as occupations and herbicides, pesticides, and fertilizers as exposures, have yielded inconsistent results.[6] For each study showing increased risk,

[1] M. Belson et al., 2007, *Environ Health Perspect* 115:138-145.
[2] C.S. Rubin et al., 2007, *Environ Health Perspect* 115:151-157; K.K. Steinberg et al., 2007, *Environ Health Perspect* 115:158-164
[3] G. Spivey et al., 2006, www.cdc.gov/nceh/clusters/sierravista/SierraVistaReportOnly.pdf
[4] http://www,fhcrc.org/research/diseases/aml/
[5] http://www.atsdr.cdc.gov/toxprofiles/tp3.html
[6] J. Dreiher and E. Kordysh, 2006, *Acta Haematol* 116:153-164.

there are several studies showing no increased risk. The balance of evidence is against farming, ranching, herbicides, or pesticides increasing the risk of leukemia.

Lymphoma and Mulltiple Myleoma

Cells derived from lymphoblasts normally undergo development and maturation in the bone marrow (B cells and Natural Killer cells) or in the thymus gland (T cells). In both Hodgkin and non-Hodgkin lymphoma, abnormal cells may be present in the circulation or they may invade the body's lymph system such as the lymph nodes, thymus, spleen, or tonsils. In multiple myeloma, abnormal B cells accumulate in the bones throughout the body, typically forming many discrete tumors. Lymphoma and myeloma are rarely diagnosed in children although Hodgkin lymphoma is most commonly diagnosed in patients between ages 15 and 30 (Figure 4). Non-Hodgkin lymphoma and multiple myeloma are more commonly diagnosed after age 45.



Family history is a risk factor for all three of these types of cancer. In addition, many cases of Hodgkin and non-Hodgkin lymphoma are associated with a history of Epstein-Barr virus infection. However, approximately 80% of the US adult population has had an Epstein-Barr infection so the virus alone is not a sufficient cause of lymphoma. Most cases of Epstein-Barr virus infection are asymptomatic or perhaps attributed to a cold or mild flu, although some people develop mononucleosis. It is not clear why the Epstein-Barr virus persists in some people and is ultimately associated with lymphoma. Because family history is also a risk factor, it is possible that the virus interacts with a genetic predisposition in some people. A history of autoimmune disorders and chronic inflammatory conditions are risk factors for multiple myeloma and these conditions may also reflect a genetic predisposition to developing this kind of cancer.

Radiation exposure among atomic bomb survivors is a risk factor for non-Hodgkin lymphoma and multiple myeloma, as is a history of therapeutic radiation, but these do not appear to be risk factors for Hodgkin lymphoma. Occupational exposure to two classes of chemicals (organochlorine insecticides and chlorophenol fungicides, wood preservatives, and herbicides) may be risk factors for non-Hodgkin lymphoma and some pesticides are suspected risk factors for multiple myeloma, but these associations were not found in all studies.[7]

Summary

The hematological cancers -- leukemias, lymphomas, and myeloma -- are uncommon cancers as a group and individually some are rare. Each type has its own age distribution and set of known or suspected risk factors. For most patients, it is not possible to point to a single exposure or risk factor that caused the cancer, although for some a history of exposure to a known risk factor can be identified. The early childhood incidence of ALL and adolescent incidence of Hodgkin lymphoma are especially striking. In spite of many studies of suspected risk factors, no explanations for these unusual childhood cancers are available and genetic predisposition is suspected in many cases.

Please visit our website at www.cancer.mt.gov

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[7] J. Dreiher and E. Kordysh, 2006, *Acta Haematol* 116:153-164.